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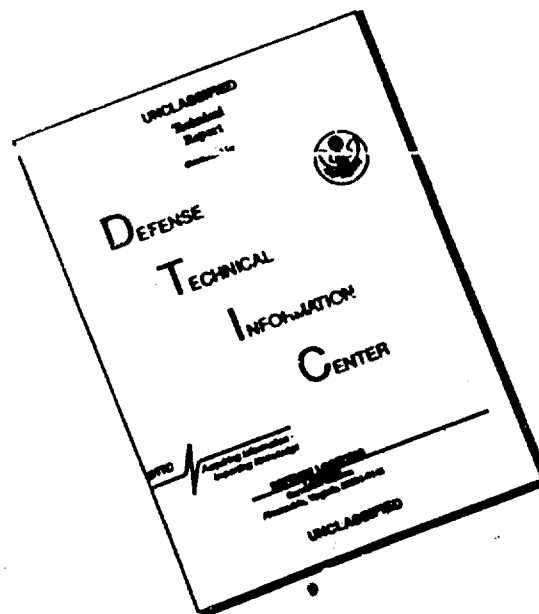
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Infectious Diseases)

Pathogenic Diagnosis and the Therapy of Botulism

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The theory about toxoinfectious nature of botulism was supplemented in recent years by many new and highly decisive data that enabled us to draw important practical conclusions. The beginning of these observations was established in 1933, during a great flareup of botulism (Dnepropetrovsk). A detailed analysis of the clinical, laboratory and pathoanatomical observations made during the flareup was sufficiently convincing to regard botulism as a toxoinfection, instead of pure intoxication. The prewar research carried out in laboratories under our supervision proved conclusively that botulinal toxin is the basic factor involved in the toxoinfectious function. If botulinal toxin is admitted to an organism of experimental animals in nonfatal doses together with microbes of botulism, it "sensitizes" the animals, consequently the botulism microbes begin to multiply and to produce additional toxin to that already present in foodstuffs.

However, still unexplained remained the question about the mechanism of the "sensitizing" effect of botulinal toxin and about

a site of the basic production of botulinal toxin in infected organism.

In the postwar period we continued the investigation of the two questions in laboratories under our supervision. It was found that one characteristic of botulinal toxins (we studied types A, B, C and E toxins) was their suppressive action on the phagocytic function of leukocytes. This characteristic of botulinal toxins could be readily determined by their action on leukocytes of the blood in vitro and particularly in animal organs.

Following the administration of some fatal doses of the toxin to an organism, the phagocytic index (which is a criterion of the phagocytosis activity) may drop to zero, although a toxic effect is also clearly expressed after administration of nonfatal doses. A suppressed phagocytic effect is particularly clearly expressed if we consider the toxin of the A, B and C types; less, if we deal with the toxin type E. Following the administration of toxin to an organism, the suppression of phagocytosis begins already after 2 to 3 hours, while the symptoms of botulism are completely absent in animal, i.e. during the incubation period of the disease.

A number of the phagocytic index returns almost to normalcy, if a typical antitoxic antibotulinal serum is added to a test tube during determination of the phagocytic index; this, however, was not observed when antitoxic serums of different types were added. This circumstance provides an opportunity for detection of not only the botulism disease as such, but also the botulinal type with the aid

of the phagocytic index of leukocytes in the blood of botulism patients and in those, who are suspected of having botulism; thus, it is important to a rational therapy.

The Ministry of Health of the USSR issued instructions to a special committee working in the laboratory under the supervision of prof. K.I. MATVEEV (GAMALEI'S Central Institute of Epidemiology and Microbiology) to check in a practical way the potentiality of the characteristic discovery in botulinal toxins, namely their suppression of phagocytosis in the blood of leukocytes. The prepared instructions how to utilize the method of determination of the phagocytic index in diagnosis of botulism were approved by the chief state inspector of the Ministry of Health of the USSR and were later published for effective utilization. Subsequently, research papers appeared that confirmed the effectiveness of the method, which was tested on botulism patients (L.G. KOVTUNOVICH, A.E. ESSEI, YU. I. DONETS, etc.).

Following our proposition, YU.I. DONETS studied the problem of the effect of botulinal toxin on the reticuloendothelial system. The observations proved that a considerable suppression of the absorbing function existed in cells of the reticuloendothelial system in animals under botulism intoxication and this also helped to clarify the understanding of the mechanisms that determine the toxoinfectious character in the pathogenesis of botulism, as well as the "sensitization" of the organism by botulinal toxin.

The observations relevant to a site of the production of botulinal toxin in infected organs were carried out in laboratories under

our supervision by L.M. SHVXDOV. They clarified the problem of intravital and posthumous findings pertinent to botulinal toxin in various organs and tissues. Two facts attracted our attention: 1) a frequent detection of botulinal toxin in the digestive tract, especially in the small intestine of cadavers of patients who died from botulism several days after ingestion of infected foodstuffs (5 to 10 or 12 days), whereas, it is well known that pure botulinal toxin, administered perorally without microbes to experimental animals, is usually detected there after few hours; 2) one can frequently find botulinal toxin in the blood of patients stricken with botulism; as a rule, the toxin disappears after a suitable type of antitoxin serum is administered to the patient. Yet, with the adverse course of botulism disease, botulinal toxin reappears in the blood several hours after administration of serum.

It was necessary to explain the origin of these phenomena, because they indicated that in the organism of a patient certain factors exist, which condition a prolonged presence of the toxin in the digestive tract and, as the toxin is constantly absorbed into the blood, this causes a prolonged intoxication in the organism, and also the reappearance of botulinal toxin in the blood.

If one proceeds from a supposition that botulinal microbe in infected organism strengthens the pathogenic characteristics by "sensitizing" the organism with botulinal toxin, one can understand a prolonged presence of botulinal toxin in intestines of infected organisms and the reappearance of toxin in the patient's blood, although the antitoxic serum was administered to him.

Hence, even in the prewar period we made attempts to neutralize botulinal toxin with antitoxic antibotulinal serum administered into digestive tract. Observations were carried out in laboratories on infected animals under experimental conditions, as well as on patients stricken with botulism. The observations indicated that antitoxin administered perorally to healthy laboratory animals could be detected several days later in the lower section of the small intestine; also, when animals were exposed to peroral administration of botulinal toxin, and received antitoxin, this entrained the neutralization of the toxin in the digestive tract.

We also accomplished effective treatment of seven patients stricken with botulism by giving them antitoxic antibotulinal serum, which was administered not only parenterally, but also directly into the small intestine with the aid of duodenal catheter. All seven patients recovered, and a strongly marked improvement coincided with the time of administration of serum to these patients by means of catheter. Our colleague, N.M. SHVEDOV obtained very convincing results that confirmed the discussed method of administration of serum in cases of botulism. After he administered perorally pure botulinal toxin to one group of experimental animals and to another group the same dose of toxin together with botulinal microbes, he proved that, in the first group, pure toxin disappeared quickly from the intestines and, in the other group, the toxin lingered for days, even weeks, in the intestines of animals that received the toxin perorally together with botulinal microbes. The attention was drawn to the fact that the recovery of animals infected with the toxin and with botulinal

microbes was by far more difficult. Thus, the new findings are highly significant, because: 1) they undoubtedly indicate that a production of new doses of toxin by botulinal microbes takes place in intestines in addition to the toxin admitted to the organism with the ingestion of spoiled foodstuffs; 2) they explain the presence of botulinal toxin in the contents of intestines in patients who were stricken with botulism, and also in those who died from botulism several days after ingestion of spoiled foodstuffs; 3) the production of toxin in intestines during botulinal toxoinfection explains the reappearance of toxin in the blood of botulism patients, who for a brief time experienced the absence of toxin after administration of antitoxic serum; 4) they substantiate the necessity of administration of antitoxin to botulism patients not only parenterally, but also with the aid of duodenal catheter directly into the small intestine. We shall quote here some experimental observations made by L.N. SHVETSOV.

Since it was impossible to administer therapeutic serum into rabbits' duodenum by catheter, the author prepared a method of a special surgical approach to duodenum. Thus, tunica serosa of the intestine was sutured to the parietal peritoneum at a site, where a small incision was made through peritoneum and through other layers of the abdominal wall. Owing to this, it was possible without opening the lumen of the intestine to administer antitoxin serum with a syringe directly into the cavity of the duodenal intestine. We made observations on 56 rabbits. In this number 19 rabbits did not receive serum treatment after the infection (15 died); 19 rabbits

received only a parenteral administration of serum (10 died); 18 rabbits received a serum treatment by a combined method (2 died).

YU. I. DONETS carried out experimental studies in our laboratories and they involved the isolation of botulinal toxin from the urine of infected animals. Using the phagocytic index method for detection of toxin in the urine, the author drew a conclusion that "caffeine and theophylline administered to animals under botulinal intoxication conditions alleviated the course of their disease and frequently protected from death such animals, which received 1 Dlm of the toxin"^{*)}. At the same time, the author detected with a greater constancy the toxin in the urine of the "caffeine" group of animals, which were given diuretics, while the incidence of the toxin's detection was only sporadic in animals that received no diuretics. These observations agree with the opinion of many authors, including those of old reputation, who attach importance to renal eliminations in cases of infectious diseases, and thus recommend the intake of large quantities of liquids in order to increase the diuresis in patients.

Since determination of the phagocytic index for diagnostic purposes of botulism lasts altogether approximately three hours, it is desirable to use this method along with specifications of the biological test when a laboratory diagnosis of botulism is determined.

All botulism patients should be given a serum therapy ad-

*) - YU.I. DONETS. Sbornik Trudov Odessk. Med. Inst., vol. XIII, 1960, p.148.

administered in two ways: intramuscularly and by means of duodenal catheter. The administration of serum by both methods should begin as early as possible, because the administration of serum by means of duodenal catheter may be difficult after a subsequent advancement of myogenic paresis in the soft palate. The quantity of administered serum and the frequency of its administration, are determined by the patient's condition and they should conform with recommendations quoted in the literature and in handbooks. The administration of serum into duodenum should take place at least once a day; if the patient's condition permits and he suffers from acute intoxication, this method of administration of serum should be followed twice in 24 hours. The effects of a combined (parenteral and with catheter) administration of serum become noticeable even after 24 hours. If there is no improvement in patient's condition, serum should be applied with a catheter also on the next day.

The dose of serum administered by means of duodenal catheter should correspond to the dose of serum administered intramuscularly. The serum administered with a catheter should be diluted in two or three containers of chilled boiled water. This will assure the flow of serum to the most possible distant site in the small intestine and also a more complete neutralization of botulinal toxin, if the latter is present in the intestine. A mixture of available types of antitoxic serums should be administered prior to determination of the type of botulinal toxin, while a monovalent suitable serum should be applied right after the type of toxin had been determined.

One should have no apprehension that a digestion of serum protein can occur in the digestive tract and thus a destruction of anti-toxin may result. Observations made in our laboratories indicate that, a parietic condition of the intestine, which is observed during botulism, is accompanied by a considerable decrease in the quantity of liberated digestive juices.

If, due to some reason, serum cannot be administered to a patient with the aid of a duodenal catheter, it can be given to him in a dilution (0.5% solution of bicarbonate of soda) directly per os. Observations made under experimental conditions proved that serum administered in this way was also effective, but its therapeutic reaction has been less adequate when compared with the reaction of serum administered into duodenum.

It is recommended that botulinal patients be also administered diuretics.

Summary (copied)

Results of research work of the botulism laboratories headed by the author are summarized. It was found that botulism toxins possess the capacity to suppress the phagocytic activity of leukocytes and the absorptive function of the reticuloendothelial system. This suppression may be easily controlled by typical antitoxin sera, which is not observed under the effect of nonspecific sera. For quicker diagnosis it is recommended to determine the phagocytic index of leukocytes. The efficiency of the combined parenteral and through a duodenal probe administration of serum is established.